REMARKS

I. Status of the Claims

Claims 26 and 30-50 are pending in the application, claims 1-25 and 27-29 having been canceled. Claims 30-50 are withdrawn, claims 51-53 have been added and claim 26 has been amended above. Support for the amendment to claim 26 can be found in Example 1 on page 20, lines 9-20. Claim 26 is under examination and stands rejected under 35 U.S.C. §112, first paragraph and under 35 U.S.C. §103 over Dorken *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 26 is rejected as allegedly lacking enablement for compositions where the multimeric form is no more than 3% of the total combined weight of multimeric and monomeric forms. In coming to this conclusion, the examiner relies heavily on applicants' own Table 1 from the instant specification. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to remove the % multimer recitation. In addition, the attached (second) declaration from Dr. Thomas Urbig explains:

> 8. I also wish to clarify that Table 1 on page 26 of the present application does not disclose data of approximate percentages of monomers and dimers present in the specific single chain monoclonal antibodies produced by the method of the present invention. The data presented in Table 1 was obtained from the analysis of the harvested supernatant containing secreted polypeptide after the cells producing the polypeptide are separated from the culture media as disclosed in the first paragraph of Example 1, on page 19 of the above-identified application. A closer review of Example 3, beginning with the text on page 25 supports that bispecific antibodies were produced in CHO cells according to known methods, and then this supernatant was analyzed to determine the proportions of polypeptide in monomeric and dimeric form as determined by SDS-PAGE performed under reducing conditions, Western Blot and gel filtration. Table 1 was included in this application to show the percentage of dimers of the polypeptides that form when secreted by the cells and before purification according to the methods of the present invention.

The sentence following Table 1 further supports my statements, and particularly, the phrase "spontaneously forms" further clarifies that the polypeptide that was tested was obtained directly from the CHO cells without purification:

> As can clearly be seen in Table 1, each bispecific single chain antibody with anti-human CD3 antigen binding specificity spontaneously forms significant amounts of multimeric (i.e., dimeric) species when left uncontrolled.

Therefore, I confirm that the percentage of dimers disclosed in Table 1 does not reflect the percentage of dimers present in polypeptide preparations purified according to the methods of the above-identified application, and therefore, does not appear to be relevant to the Examiner's lack of enablement rejection of the claimed composition.

Reconsideration and withdrawal of the rejection, in light of these comments and the attached declaration, is therefore respectfully requested.

III. Rejection Under 35 U.S.C. §103

Claim 26 is rejected as obvious over Dorken *et al.*, U.S. Patent 7,112,324. The examiner argues that Dorken provides for "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen." While Dorken is admittedly silent on percentage of multimers, it is argued that such would be met by Dorken's disclosure of standard purification techniques such as imidazole gradient, gel filtration, cation exchange chromatography, and gel electrophoresis. Once again, applicants traverse.

At the outset, applicants submit that the examiner has not established a *prima facie* case of obviousness. The prior art admittedly fails to teach each element of the claimed invention, and no evidence has been provided showing why that element is obvious or inherent in the cited or any uncited art. Moreover, the claims as amended herein provide additional recitations of citrate buffer and lysine that further distance the present invention from Dorken. However, in the interest of advancing the prosecution, applicants also provide the second declaration of Dr.

Thomas Urbig (attached), which provides evidence of surprising and unexpected results for the invention as now claimed.

As explained by the declarant, the composition of the present invention contains a polypeptide comprising at least two antigen binding sites (human CD3 and human CD19) as claimed in SEQ ID NO:1, (hereinafter referred to as "Construct 1") and a citrate buffer containing lysine. The declarant explains in paragraph 5 of his declaration the rationale for developing an improved formulation for Construct 1 based on the instability data of Construct 1 in phosphate buffered saline over time and the removal of the undesired excipient, human serum albumin. As stated in Dr. Urbig's declaration, the citrate buffer was selected based on testing that showed that monomer recoveries of Construct 1 are more stable in citrate buffer at pH 5.5, 6.0 and 6.5 as measured by SEC-HPLC as compared to monomer recoveries of Construct 1 contained in phosphate, histidine or succinate buffers in the pH ranges of 6.0 to 7.5. Thus, based on this experimental data, Dr. Urbig concludes that the presence of citrate buffer in a composition containing Construct 1 provides improved and unexpected stability of monomeric Construct 1 as compared to Construct 1 in the other tested buffers.

Further, with regard to the inclusion of lysine in the buffer of the claimed composition that contains Construct 1, Dr. Urbig explains that the experimental data shows that lysine stabilizes Construct 1 monomers as measured by SEC-HPLC as compared to Construct 1 incubated in the presence of other amino acids. Thus, the presence of lysine in the buffer also provides improved and unexpected stability of monomeric Construct 1 as compared to the other tested amino acids.

Based on these data, Dr. Urbig opines that a composition containing Construct 1 in combination with a buffer comprising citrate and lysine possesses improved stability of the

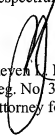
monomeric form of Construct 1 over time, which is an unexpected result as compared with known buffers and other amino acids tested. Thus, even if a *prima facie* case of obviousness had been made out, these data would effectively rebut it.

Reconsideration and withdrawal of the rejection, based on the preceding comments and attached declaration, is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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